



## The role of the cysteine proteinase cathepsin S in astrocytoma invasion

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Macrophages were distributed throughout the tumour, but were increased around areas of necrosis and around blood vessels. No relationship between tumour cell proliferation and necrosis was detected. **Conclusions:** Tumour cell proliferation is concentrated around blood vessels in glioblastomas. Blood vessel proliferation, but not tumour cell proliferation, is related to areas of necrosis and the presence of macrophages in glioblastomas. Targeting of blood vessel proliferation and macrophages within glioblastoma may present a therapeutic strategy for treatment of these devastating tumours.

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#### **Loss of chromosome 10, retinoblastoma and deleted-in-colon-carcinoma (DCC) proteins in glioblastomas**

**Introduction:** Glioblastomas have a median survival of 9–12 months. However, some patients die within a few weeks of diagnosis and others may survive for 2 years or more. To try to predict survival more accurately, we have evaluated a number of morphological, immunohistochemical and molecular markers in a retrospective series of glioblastomas. **Material and methods:** Paraffin sections from 107 consecutive glioblastomas diagnosed between 1993 and 1997 were included in the study. All cases were reviewed and the presence of calcification or oligodendroglioma-like areas noted. Sections were immunostained with commercial antibodies to retinoblastoma and DCC proteins and subjected to *in situ* hybridization with probes to chromosomes 12 and 10. **Results:** Loss of retinoblastoma and DCC protein expression was seen in 20% and 71% of glioblastomas respectively. Loss of retinoblastoma protein expression correlated with poor outcome ( $P=0.045$ ). 64% of glioblastomas showed loss of chromosome 10 but this did not have a significant association with survival. The five tumours with oligodendroglioma-like areas had a median survival of 70 weeks, compared with 27 weeks for those without ( $P=0.014$ ). **Conclusion:** In this study, age, loss of retinoblastoma protein and a lack of oligodendroglioma-like areas were predictors of significantly shorter survival in glioblastomas.

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#### **The role of the cysteine proteinase cathepsin S in astrocytoma invasion**

**Introduction:** Local tumour invasion gives rise to recurrence after surgical resection, leading to the poor prognosis associated with malignant astrocytomas. Extracellular proteolytic enzymes including cysteine proteinases have been implicated in facilitating tumour cell invasion. The current study was designed to characterize the expression of the cysteine proteinase, cathepsin S and investigate its potential role in the invasive process. **Materials and methods:** Expression of cathepsin S was investigated in astrocytoma biopsies by immunohistochemistry and in astrocytoma cultures by immunocytochemistry and the reverse transcription polymerase chain reaction. Cathepsin S activity assays were also performed on *in vitro* and *in vivo* samples. An *in vitro* Matrigel invasion assay was used to evaluate the effect of selective cathepsin S inactivation, by the inhibitor LHVS, on glioblastoma cell invasion. **Results:** Cathepsin S immunostaining was restricted to tumour cells *in vivo*. Cathepsin S transcript, protein and activity were observed within astrocytoma cells *in vitro*. Extracellular cathepsin S activity was about five-fold higher in cultures from grade IV tumours than in lower grades. Inhibition of cathepsin S with 0.01  $\mu\text{M}$  LHVS significantly inhibited *in vitro* invasion of the glioblastoma cell line U251 mg by 50% ( $P<0.0001$ ). **Conclusions:** It has been demonstrated for the first time that cathepsin S is expressed and secreted by astrocytoma cells and plays a role in astrocytoma invasion, and is therefore a potential therapeutic target.

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#### **The expression of the EGF receptor family and their ligands in human medulloblastomas**

**Introduction:** Little is known about the molecular processes behind the development of medulloblastomas.